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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/621,715	MORI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,10,12,13 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 5, 10, 12, 13, and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-3, 6-9, 11, and 14 are cancelled.
Claims 1, 4, 5, 10, 12, 13, and 15-22 are pending and examined on the merits

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/01/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 02/01/2007. Claim(s) 2-3, 6-9, 11, and 14 is/are cancelled; no claim(s) is/are withdrawn; no claim(s) has/have been newly added; claim(s) 1, 10, and 18 has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

Response to the Declaration Under 37 CFR 1.132

1. The Declaration under 37 CFR 1.132 filed 02/01/2007 is insufficient to overcome the rejection of claims 1, 3-5, 10, 12, 13, 15-18, and 19-21 based upon the teachings of Morishita et al (US Pat 4,118,336) as set forth in the last Office action because:

The Declaration asserts that the methods of Morishita et al are not effective in the purification of a nucleic acid because when Applicant attempted to filtering a solution containing the particles as taught by Morishita using a glass or paper filter the method could not be performed because the particles clogged the filters. It is noted that Applicant did successfully use the particles to purify a DNA molecule using centrifugation to separate the particles from a solution. The Declaration is not sufficient to show inoperability of the method made obvious by Morishita et al because the claims do not require to separation of any particles using a filter. Additionally, Applicants Declaration shows only that some particular filters were not useful in the separation of particles taught by Morishita et al, not that there is no way to separate the particles of Morishita et al using other filters (e.g. filters with larger pore sizes) or filtering techniques (e.g. use of a pre-filter) that are well known to one of skill in the art. Furthermore, to attempt the method described in the instant Declaration using glass or paper filters is to ignore the various teachings of Morishita et al that particles are filtered with a cloth filter (col.8 - Example 8) which may afford a larger filter pore size thus allowing for filtering without clogging.

Applicants have also argued (pages 9-10 of Remarks) that the Declaration provides evidence of unexpected results. However, if applicants intend to argue that an unexpected result is provided in the purification of DNA using particles separated by centrifugation, it is noted that the instant claims do not require, and the instant specific does not provide support for, any methods specifically requiring the step of centrifugation of particles.

It is noted that the rejections of claims based on the teachings of Morishita et al as presented in the Office Action of 11/01/2006 are withdrawn in light of the amendments to the claims.

Response to Remarks concerning Rejections Under 35 USC 103

2. Applicants have traversed (pages 8-10 of Remarks) the rejection of claims under 35 USC 103 as obvious in view of the teachings of Morishita et al.

Applicants have argued (pages 9-10) that the Declaration provides evidence of unexpected results. The ineffectiveness of the Declaration has been detailed above.

Applicants have amended the claims to require a pore size of 0.1 μm to 10 μm and argued that such a limitation is not taught by Morishita et al (page 9 of Remarks). This argument is persuasive; the rejection of claims in view of the teachings of Morishita et al are withdrawn and new grounds of rejection are set forth.

Claim Rejections - 35 USC § 103

In the rejection of claims under 35 USC 103, the required limitations of the claimed methods are noted. The base claim (i.e. claim 1) has been amended to include the limitation that the method comprises a step of 'selecting a rate of surface saponification and pore size of a solid phase, said solid phase being a porous film of a surface-saponified triacetylcellulose' and requires that 'the surface-saponification rate of the triacetylcellulose id 10 to 100% and the pore size of the porous film is 0.1 um to 10 μm'. The current claims do not require, for example, selecting a length of a nucleic acid to be purified from a nucleic acid sample solution containing nucleic acids of different lengths, and selecting a rate of surface saponification and pore size of a

triacetylcellulose film such that the saponification rate and pore size are suitable separation and purification of the said nucleic acid to be purified.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 4, 5, 10, 16, 17, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of Tsao et al US Patent 4,090,022 (1978).

Kitos et al teaches separation of nucleic acids using solid phase cellulose (p.5807, left col., lns.13-25).

Regarding claim 1 Kitos et al teaches adsorbing nucleic acid of a predetermined length (p.5807, left col., lns. 48-50), where the nucleic acid is for example [^{3}H]poly(A) with a minimum molecular weight of 5 X 10^4 daltons which is approximately 150 bases in length, to a solid phase of cellulose wherein a nucleic acid solution contains nucleic acids of different lengths (Table 1; p.5807, left col., lns.41-62). Kitos further teaches washing the solid phase (p.5807, left col., lns.26-30; Figure 1 legend) and desorbing the nucleic acid (p.5807, left col., lns.37-40; Figure 1 legend). Kitos teaches the purification of the nucleic acid from the mixture (see for example Table 1, last data row, where [^{3}H]poly(A) in a mixture of poly(A0) and poly(U) is eluted in Buffer K.

Regarding claim 16, Kitos et al teaches elution buffer having a salt concentration lower than 0.5M (p.5807, left col., lns.37-40).

Regarding claim 17, Kitos et al teaches chromatography using a cellulose in a column (p.5807, left col., lns.15-25), which is a unit having two openings (at the top and the bottom) that contains the solid phase.

Regarding claim 21, Kitos et al teaches separation of a nucleic acid that is [^{3}H]poly(A) with a minimum molecular weight of 5 X 10^4 daltons, where such a nucleic acid is approximately 150 bases in length.

Kitos et al does not teach the use triacetylcellulose with a surface saponification of 10-100% and a pore size of 0.1 μm to 10 μm.

Tsao et al teaches porous cellulose beads for the separation of nucleic acids (col.2 lns.26-28 and lns.51-53).

Regarding the limitations of claim 1, Tsao et al teaches that beads may have pore sizes ranging from 0.05 to 30 μm (col.7 lns.17-18), and specifically that pore sizes of beads can be 1,000 Angstroms (col.3 lns.47-51) which is 0.1 μm. Tsao also teaches (col. 11 – Example V) using beads made from cellulose triacetate where the beads are treated with 0.15 N sodium hydroxide overnight at room temperature (as in col.10 Example I), where such a treatment results in a porous bead with a center of cellulose triacetate and a surface of cellulose triacetate having 10 to 100% saponification (i.e. saponification is deacetylation of the cellulose) on the surface.

Regarding claims 4 and 5, the deacetylation procedure of Tsao et al (.15 N sodium hydroxide overnight at room temperature as in col.10 Example I) results in a surface saponification rate 5% or higher (claim 4) and 10% or higher (claim 5).

Regarding claim 10, the procedure of Tsao et al of creating a cellulose triacetate bead followed by deacetylation results in saponified triacetylcellulose coated on a bead of cellulose triacetate.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the porous beads made of cellulose triacetate taught by Tsao et al for the purification of nucleic acids using the methods taught by Ktios et al. One would have been motivated to use the beads of Tsao et al because Tsao et al teaches that such beads offer enhanced flow properties (col.11 lns.24-44) and Kitos et al uses column based methods that require fluid flow.

5. Claims 12, 15, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of Tsao et al US Patent 4,090,022 (1978) and further in view of Woodard et al (EP 0512767).

The teachings of Kitos et al in view of Tsao et al are applied to claims 12, 15, and 18 as they were previously applied to claims 1, 4, 5, 10, 16, 17, and 21.

Kitos et al in view of Tsao et al teaches the separation of a nucleic acid from a solution containing a mixture of nucleic acids using porous surface-saponified cellulose triacetate.

Kitos et al in view of Tao et al does not teach making a sample solution with organic solvents ad solubilizing reagents (claim 12), wash buffers with alcohols (claim 15), or a pressure difference generating apparatus (claim 18).

Regarding claim 12, Woodard et al teaches a steps of treating a sample containing a cell or a virus with a nucleic acid solubilizing reagent (i.e. a lysis buffer) and then preparing the sample solution by adding an aqueous organic solvent to the solution. Specifically, Woodard et al teaches that DNA is obtained in such a way that the procedure ends with a suspension of DNA in a solution such as a lysate, a step which includes treating the sample with a solubilizing reagent (p. 3, lines 3-13). Woodard et al also teaches the subsequent addition of an organic solvent to the solution (p. 3, lines 19-22).

With regard to claim 15, Woodard et al teaches the nucleic acid washing buffer that contains 50% ethanol, for example (p. 3, line 24).

With regard to claim18, Woodard et al teaches the use of a unit with a blotter which 'pulls liquid through a membrane' (p. 9, lines 5-15).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Woodard to provide nucleic acid and apparatus of Woodard in the separation of nucleic acids according to the methods of Kitos et al in view of Tsao et al. One would have been motivated to use the reagents and methods of Woodard et al based on the teachings of that such methods can successfully purify nucleic acids, and the teachings of Kitos et al that such nucleic acids may be purified form cellular sources (p.5091, right col., last paragraph).

6. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of Tsao et al US Patent 4,090,022 (1978) and Woodard et al (EP 0512767), and in further view of Benjamin et al US Patent 5,695,946.

The teachings of Kitos et al in view of Tsao et al and Woodard et al are applied to claim 13 as they were previously applied to claims 12, 15, and 18.

Woodard et al teaches using "typical" procedures for obtaining DNA from samples (p. 3, lines 5-6), but does not teach a step wherein the nucleic acid solubilizing reagent comprises a guanidine salt, a surfactant, and a proteolytic enzyme.

Benjamin et al teaches that target nucleic acid molecules are released from cells by treatment with any number of reagents, including guanidine salts, proteinase K and detergents (Col. 8, lines 7-12). Benjamin et al exemplifies the use of the surfactant SDS for cell lysis (Col. 12, line 15).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have have modified the methods of Kitos et al in view of Tsao et al and Woodard et al, so as to have utilized a lysis buffer that included reagents that are typically considered lysis agents for the release of nucleic acids from sample cells. One would have been motivated by the teachings of Woodard et al that any such typical methodologies for obtaining lysis solutions could be used and by the teachings of the Benjamin et al that each of these reagents are commonly used for the lysis of cells.

7. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitos et al (1973) in view of Tsao et al US Patent 4,090,022 (1978) and Woodard et al (EP 0512767), and in further view of Heath WO 99/13976.

The teachings of Kitos et al in view of Tsao et al and Woodard et al are applied to claims 19 and 20 as they were previously applied in the rejection of claims 12, 15, and 18 previously in this Office Action.

Heath teaches methods for isolation of nucleic acid from samples and teaches automated steps of loading a sample into a container with at least two openings (p. 7, lines 11-12), loading a wash into the container (p. 7, lines 13-17), and loading desorbing buffer (referred to as elution buffer) into the container (p. 7, lines 18-23). Heath teaches the use of vacuum pumps for the movement of solutions into and out of the isolation chamber (p. 8, lines 6-14; 21-22). Heath specifically teach that methods in which the sample is loaded via aspiration which occurs via the insertion of the opening of the chamber into the sample and the application of negative pressure to suck the sample into the chamber (p. 10, exemplified p. 23). Further, Heath teaches methods in which the gases are pumped into the chamber which increases pressure in the chamber and forces fluid out of the chamber (p. 12, lines 13-15).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Kitos et al in view of Tsao et al and Woodard et al, to include the sample processing methodologies taught by Heath. One would have been motivated to apply the methods of Heath to the methods taught by Kitos et al in view of Tsao et al and Woodard et al in order to have provided

methods for applying the fluids necessary to practice the methods taught Kitos et al in view of Tsao et al and Woodard et al to the solid supports for the isolation of nucleic acids.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4, 5, 10, 12, 13, and 15-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some amount of separation of a 1.3kb DNA fragment from a 48kb DNA fragment in a mixture containing said DNA fragments, using surface saponified triacetlycellulose, does not reasonably provide enablement for the separation of any sized nucleic acid fragments from one another from within a mixture containing any number and type of nucleic acid fragments of differing lengths using any other organic macromolecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The nature of the invention is a method for separating and purifying a nucleic acid of a predetermined length from a mixture of nucleic acids using solid phase organic macromolecule, and more specifically using a porous membrane consisting of surface saponified triacetlycellulose. Alteration of the surface saponification rate of

acetylcellulose and the size of the pores in a film made from the compound allows for the adsorbing of particularly sized nucleic acids, and their subsequent purification by desorbing. The nature of the invention requires knowledge of the relationship of the surface saponification rate and pore size of a film of cellulose triacetate with recovery rate of any particular length of nucleic acid.

The claims encompass the separation and purification of any type of nucleic acid (e.g. DNA or RNA) from a nucleic acid mixture of any complexity (i.e. containing any amount of nucleic acids of any length). The claims encompass the use of any surface saponification rate between 10 to 100%, and any pore size between 0.1 μm to 10 μm.

State of the prior art, level of skill, and level of unpredictability

While the level of skill in the art of nucleic acid separation is high, the state of the prior art with regard to nucleic acids binding to acetylcellulose indicates a high level of unpredictability. The prior art does not teach any correlation between particular saponification rates or pore sizes and the ability of an organic macromolecule to separate nucleic acids of specific lengths from mixtures of nucleic acids.

Several references teach that cellulose acetate membranes will not bind to DNA. GE Osmonic (1997) teaches the use of cellulose acetate membranes to filter nucleic acid probes, indicating the membrane is ideal because it is a non-DNA binding polymer. Similar statements about cellulose acetate are taught in two recent references: Corning (2005) indicates that cellulose acetate is inert, and does not bind either DNA or protein, and Whatman (2005) indicates that ability of DNA to bind to cellulose acetate is 'very low'.

It is also unpredictable how the sequence of any particular DNA might affect its ability to be separated in a size dependant manner using the methods described by the instant specification. Yang et al (1998) teach that DNA molecules with particular sequences (Table 1, p.5465) can bind tightly and specifically to cellulose. It would therefore be unpredictable how the presence of any of the indicated 'cellulose-binding DNA aptamer' sequences, within a larger nucleic acid sequence, would affect the separation of the nucleic acid by the method of the instant application regardless of the saponification rate or pore size of a medium containing an organic macromolecule with hydroxyl groups.

Van Oss et al (1987) indicate the unpredictability of different nucleic acids (e.g. DNA versus RNA) binding to acetylcellulose. The reference teaches that while interaction between DNA and cellulose esters can be considerable, the binding energy of RNA to cellulose esters is low (p.53). Table IV (p.60) indicates the clear difference in free energy of adhesion of DNA on cellulose acetate versus RNA on cellulose acetate; the reference teaches that DNA should bind more strongly to cellulose esters that RNA (p.61), and RNA is much more weakly attracted to cellulose esters than DNA (p.63). Pan et al (2003) teaches the inherently different structural properties of DNA versus RNA. The reference indicates that different chemistries of DNA and RNA allow for different flexibilities and the adoption of different conformations, thus making it unpredictable as to how these different molecules would interact with the membranes (i.e. varying saponification rates and pore sizes) discussed in the instant application.

Direction provided and presence of working example

The instant specification asserts that nucleic acids can be separated and purified by preparing a plurality of porous membranes with varying surface saponification rates and varying pore sizes. The specification provides data regarding the recovery rate of two DNA fragments (1.3kb and 48kb) from various preparations of triacetylcellulose (p.28, Tables 3 and 4; Fig 5). The specification teaches that recovery rate (that is the percentage of the DNA that is applied to a membrane which is adsorbed to the membrane and then desorbed from the membrane) varies between two different saponification rates (either 50% or 100%) and four different pore sizes (0.2, 0.4, 1.0, or 2.5μm). There is no other information provided for any other saponification rates or pore sizes. Notably, there is no information contained within the specification for saponification rates lower than 50% (as are encompassed by the claims, for instance claims 4 and 5 which particularly point out saponification rates with lower limits of 5% and 10%, respectively). Similarly, there is no other information provided for any pore size other than those listed in Table 1; notably there is no information in the specification concerning pore sizes larger than 2.5μm (as are encompassed by the claims, for instance claim 9 which particularly points out pores sizes as large as 10μm).

The specification indicates (pp.10-11) the following saponification rates combined with the following pore sizes will allow the recovery (by adsorbing and subsequently desorbing) of particularly sized DNA: both low molecular weight DNA and high molecular weight DNA were recovered from 100% saponified membranes with 0.2μm pores; recovery of high molecular weight DNA is relatively higher (compared to recovery of low molecular weight DNA) from 50% saponified membranes with 0.2μm pores; the

recovery rate of high molecular weight DNA is high from 100% saponified membranes with 2.5μm pores.

The specification provides a single example of the purification of a low molecular weight nucleic acid and a high molecular weight nucleic acid from a nucleic acid mixture (pp.28-29). This example demonstrates the separation of a 1.3kb fragment from a 48kb fragment which had been mixed together in an aqueous solution. In the example, the different DNAs are separated by the sequential action of a first membrane (100% saponified, 0.2 μm pore size) and a second membrane (50% saponified, 0.2 μm pore size). And while the specification asserts that it is clear from the results of Fig. 5 (a photograph of an agarose gel) that a nucleic acid having a desired size can be purified by selecting saponification rate and pore size, there is no quantification of the results to indicate the resulting level of separation. For instance, regarding the isolation of the 1.3kb DNA (condition (c) on p.29) from a mixture containing 10μg each of a 1.3kb DNA and a 48kb DNA (as in (4) on p.27), one would expect (based on the collection rate information presented in Tables 3 and 4) for the final recovered product to contain 7.7μg of 1.3kb DNA and 1.4μg of 48kb DNA.

The specification does not provide any example of the separation of any other nucleic acid mixtures other that the 1.3kb and 48kb mixture described in Example 1, or results concerning recovery rates from any other saponification rates or pore sizes than those presented in Tables 3 and 4. It is unknown what resolution of separation would be attainable with other membrane and/or nucleic acid mixture conditions. For instance, are there any possible conditions that would allow for the separation of a 9kb DNA

fragment from an 11kb DNA fragment. Additionally, while the specification refers to conditions for purification of high molecular weight versus low molecular weight molecules, the specification refers to a 10kb fragment as both a relatively long nucleic acid (p.12 ln.1) and a relatively short nucleic acid (p.12 ln.11).

The specification does not provide any guidance concerning the separation of any nucleic acid mixtures containing anything other than the double stranded DNA of Example 1.

Quantity of experimentation required

A prohibitive amount of experimentation would be required to use the claimed invention in its full scope. For any given mixture of nucleic acids, one would have to establish the recovery rate of a nucleic acid of interest having a particular length under different saponification and pore size conditions. One would also have to determine if the described methods would be compatible RNA, or perhaps with other types of nucleic acids such as peptide nucleic acids (PNA).

Alteration of saponification rate alone would require a large quantity of experimentation. The specification indicates conditions used to achieve either 50% or 100% saponification (p.26), however there is no way to predict what conditions are needed to achieve any other saponification rates (e.g. what concentration of sodium hydroxide solution to use, and how long to treat a membrane). The specification only indicates that altering sodium hydroxide concentration can change saponification rate (p.10), and that the rate is determined by quantifying remaining acetyl groups by NMR.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and scope of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of a working examples, it is the conclusion the an undue amount of experimentation would be required to use the invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st paragraph (pages 10-13 of the Remarks). Applicants' arguments and amendments to the claims have been fully and carefully considered but are not found to be persuasive.

Applicants have argued that the prior Declaration (of 05/22/2006) provides an overwhelming amount of evidnce regarding the range of sizes of DNA that may be separated by the present invention. However, as noted earlier in the Office Action of 11/01/2006, that Declaration demonstrates separation of a 200 bp fragment and a 1,500 bp fragment, claiming there is thus evidence for separations over three orders of magnitude of size range. As addressed previously the examiner maintains that the claims require the separation and purification of a nucleic acid of a predetermined length from a sample solution 'wherein the solution contains nucleic acids of different lengths', and the claims thus encompass the separation of any sized nucleic acid from a solution containing any sized nucleic acids. Applicants Examples (from the filed specification and the Declaration) demonstrate only the separation of nucleic acids in a mixture containing short nucleic acids (200 bp, or 1,300 bp, or 1,500 bp) from very long

nucleic acids (48,000 bp). Thus Applicants characterization of the examples as teaching 'how to separate both low molecular fragments and high molecular weight fragments' and providing evidence for separations 'over three orders of magnitude of size range' does not serve to address the requirements of the claimed method.

At issue with regard to the rejection of claims under 112 1st ¶ for enablement is the resolution of separation attainable with saponified triacetylcellulose, the prediction of conditions that allow for separation of any one length nucleic acid from any other length nucleic acid, and the reliability of the performance of any prediction of conditions. Such unpredictability is further demonstrated in the prior art of Kitos et al, cited earlier in this Office Action. Kitos et al demonstrates that, for example, it is unpredictable how some sinlge-stranded polynucleotides bind to cellulose and others do not (p.5090 – Discussion).

And while the pore size limitations of the instant claims may dictate that some particularly large nucleic acid molecules are precluded by the claimed methods, it still remains that nucleic acids of small and similar sizes are clearly encompassed by the claims. For example, is one of skill in the art able to identify a priori the pore sizes and saponification rates required to separate a 1500 base pair dsDNA from a 2000 base pairs dsDNA, or from a 1700 nucleotide ssRNA? As addressed previously, the provided examples do not serve to enable one skilled in the art to separate nucleic acid of a predetermined length from a mixture or nucleic acids of similar lengths.

The rejection **is MAINTAINED.**

Double Patenting

The provisional rejections of claims for Obviousness type Double Patenting are withdrawn in light of the amendments to the claims.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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